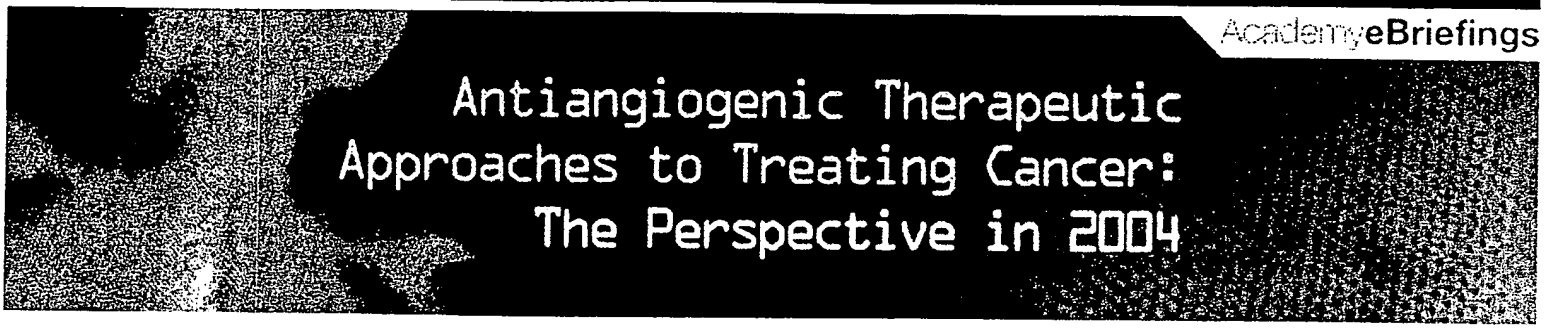

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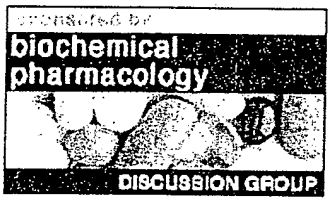

Overview

Reported by Margaret Crane | posted Apr 23, 2004

On February 26, the U.S. Food and Drug Administration approved Avastin (bevacizumab) for the treatment of metastatic colorectal cancer. It is the first drug to receive FDA approval that works expressly by blocking tumor angiogenesis, defined as the ability to generate new blood vessels. An important process in embryonic development, angiogenesis is rare in healthy adults, occurring only during menstruation and wound healing.

While Avastin is not a cure, it is being hailed as a significant advance in the long fight against cancer. Researchers committed to the antiangiogenic approach see the drug's approval as an early vindication of their central hypothesis: tumors need a reliable blood supply to grow and spread, and cutting off that supply could lead to tumor death.

The antiangiogenic approach was the topic on January 27, 2004, at *Antiangiogenic Therapeutic Approaches to Treating Cancer: The Perspective in 2004*, a meeting of the Academy's Biochemical Pharmacology Discussion Group. Marla Weetal, a co-chair of the Discussion Group, introduced the talks, and her co-organizer, Kenneth LaMontagne, concluded the discussion with a probing research agenda.

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The angiogenic switch

Curiously, most tumors never become angiogenic in the first place. The ability to attract new blood vessels is a special talent, and most human carcinomas are underachievers. The majority remain tiny, stable, and *in situ*. Their cells grow and die in balance. Ineffectual and unable to feed themselves, they're as common as they are nonthreatening to human health and longevity.

A determined minority of tumors do succeed in tipping the scales in their own favor. To outsmart the body's immune defenses, they undergo hundreds of mutations at the genomic level, acquiring critical survival skills along the way. At a certain point, the successful tumor switches from nonangiogenic bystander to angiogenic troublemaker. Able to commandeer the blood vessels it needs to grow and proliferate, a tumor may become unstoppable and, with exceptions (e.g., the benign yet highly angiogenic adrenal adenoma), malignant.

With an accretion of data and insights gleaned from more than 30 years of research, the

panelists clarified the scientific foundation for what has been termed the fourth arm of cancer treatment. (Chemotherapy, radiation therapy, and surgery are numbers one, two, and three). The speakers also brought an enthusiastic audience up to date on the latest discoveries, clinical trials, and an entirely new class of drugs—angiogenesis inhibitors—that could help win some major battles in the war on cancer, not through direct attack, but by depriving the enemy of its lifeblood.

New drugs, new targets

Instead of aiming their firepower at tumors themselves, antiangiogenic drugs target the genetically stable endothelial cells in and around the tumor bed. These normal host cells not only provide a nourishing environment for the tumor, but they may also secrete a number of proteins that stimulate tumor cell growth. In other words, they aid and abet the whole undertaking.

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Judah Folkman, widely considered the founding father of angiogenesis research, led the panel of experts. A professor of pediatric surgery at Harvard Medical School and director of the vascular biology program at Children's Hospital in Boston, he focused on the angiogenic "switch." If antiangiogenic therapeutic approaches are to succeed, ideally they should target treating cancer, in his view, before the switch even occurs.

Robert S. Kerbel, professor of medical biophysics at the University of Toronto, challenged one of oncology's most cherished orthodoxies: the idea that the maximum tolerated dose (MTD) of a drug is always the best dose. "Many oncologists believe that if a drug isn't highly toxic, it can't be working," said Kerbel. But in 2000, Kerbel and others started investigating a kinder, gentler form of treatment based on combining lower, more frequent doses of conventional chemotherapy drugs, such as paclitaxel, vinblastine, and cyclophosphamide, with newer, targeted antiangiogenic therapies. Called *metronomic chemotherapy*, it stipulates dosing schedules that mimic the regular tick of a metronome.

Stuart W. Peltz, the founder and CEO of PTC Therapeutics, described a promising antiangiogenic compound. The company has screened tens of thousands of molecules, said Peltz, and continues to make strides in understanding RNA biology—the cornerstone of its research agenda. He described how a new technology, called gene expression modulation by small molecules (GEMS), can identify compounds involved in gene expression at the RNA level.

O. Gavin Thurston, director of cancer angiogenesis at Regeneron Pharmaceuticals, shared data on his company's new drug, VEGF-Trap. It takes its name from the one meaningful target for the new angiogenesis inhibitors that has emerged thus far: *vascular endothelial growth factor* (VEGF). In addition to completely blocking new vessel growth in many established tumors, VGEF-Trap has gone beyond halting tumor growth to actually shrinking them in some preclinical studies.

Napoleone Ferrara, the pioneering Genentech scientist who co-discovered VEGF in 1989 and also led the research effort behind the development of Avastin, explained that VEGF expression occurs in the vast majority of tumors. "To be effective," he said, "angiogenesis inhibitors must suppress VEGF in both tumor-based and stromal (circulating) cells." In his talk, he discussed the shape of the molecule and the relationship between VEGF and tumor survival, as well as promising studies to date of Avastin.

Entering the mainstream

Today, there are about 30 angiogenesis inhibitors in clinical trials in the United States and 50 worldwide. For example, SU 11248, a promising Pfizer compound, blocks the VEGF receptor. The newly approved Avastin neutralizes the protein altogether.

Interestingly, several speakers pointed to the unintended antiangiogenic effects of a number of existing drugs. Herceptin, a monoclonal antibody sometimes used in late-stage breast cancer, increases the expression of thrombospondin-1, one of the body's internally-produced angiogenesis inhibitors, by 500% and decreases VEGF as well. Iressa (AstraZeneca) takes aim at VEGF by blocking its production in tumor cells.

It turns out that thalidomide, recently approved in Australia for the treatment of multiple myeloma, suppresses circulating levels of endothelial cells. Several commercially available drugs, including interferon, Celebrex (Pfizer), and Velcade (Millennium Pharmaceuticals), inadvertently block angiogenic activity. Even tamoxifen, in use for more than 20 years to fight breast cancer, has hidden antiangiogenic potential.

The human body actually produces 12 known endogenous angiogenesis inhibitors, including angiostatin, endostatin—a protein that is 600 million years old—and thrombospondin, among others. In the near future, Folkman said, small-molecule therapies may be able to prod the body's antiangiogenic proteins into action to fight tumor growth.

In the meantime, antiangiogenic therapies are inexorably entering the mainstream of cancer treatment. Clinicians are using them alone or in combination with chemotherapy drugs, radiation therapy, and surgery.

Combining old and new

Unlike older therapies, the new approaches may prove minimally toxic. High levels of toxicity are often accepted as the norm, a necessary by-product of a drug's cancer-fighting ability. Low, steady dosing based on the newer therapies may change that.

Because it appears to be endothelial cell-centric, metronomic chemotherapy comes with an even more welcome advantage, Kerbel said: "Unlike cancer cells, endothelial cells shouldn't acquire drug resistance as easily, precisely because genetically, they're stable."

In contrast to MTD, low, steady dosing also goes far toward preventing or delaying drug resistance. Extremely toxic to both cancerous tumors and healthy tissues alike, conventional higher-dose chemotherapy is administered in an all-or-nothing fashion, with several weeks between successive doses. Its anticancer effects may be dramatic in the short run, but tumors may quickly learn to bounce back, especially during breaks in treatment.

"Even patients who have relapsed will sometimes respond to the same drug administered on a metronomic schedule," Kerbel added. They may do even better, he speculated, with the addition of an antiangiogenic agent. This approach, he believes, makes good clinical as well as economic sense: "Combining older chemotherapy drugs with newer angiogenesis inhibitors provides an incentive for developing new drugs, and using older drugs keeps costs down."

All this comes as welcome news for people who have already been diagnosed with cancer—even for those with late-stage disease. But with all its present-day benefits, angiogenesis research may prove even more relevant for the eventual prevention of tumors than for their destruction after the fact.

"Combining older drugs with newer angiogenesis inhibitors provides an incentive for developing new drugs and keeps costs down."

The quest for surrogate markers

Researchers envision a time when angiogenesis inhibitors will be used to treat cancer before it becomes visible. To do that, they need to identify surrogate biomarkers that appear in the blood or urine in tandem with the appearance of tumors, even before angiogenesis truly sets in.

The search for surrogate markers is still at any early stage, but it is no quixotic exercise. Calcitonin, for example, is a known marker for medullary cancer of the thyroid—a deadly disease that, even after surgery, often recurs in the chest and results in mortality rates of 80% and up. Instead of administering late-stage treatment and consigning patients to near-certain

death, oncologists may in the future "treat" the calcitonin early on, an approach that Folkman compared to treating an infection.

"Before 1930, there used to be no way to treat an infection except surgery," said Folkman. "Doctors were always asking, 'Where's the pus'? The infection's location was all they had to go on. Today, we don't have to identify its exact location. Guided by blood tests, doctors treat infections with antibiotics, and they go down."

All this means it is time to start moving away from the location paradigm. Instead of focusing exclusively on the tumor—where it is, what it's doing, how fast it's growing—oncologists may soon be able to move toward an infectious diseases model of treatment.

An angiogenesis inhibitor could be used to treat rising markers in the blood and urine, markers that signal the presence of cancer that it still *in situ*. Once we've identified such markers, hypothesized Folkman, we may be able to thwart cancer by preventing the angiogenic switch from occurring in the first place—and ensure that tumors remain underachieving nonentities in perpetuity.

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